IDEA

INTERNATIONAL DIALOGUE
FOR THE EVALUATION OF ALLERGENS

INDUSTRY PROPOSAL FOR A JOINT WORK PLAN

DEVELOP A SHARED COMMON UNDERSTANDING OF RISK ASSESSMENT METHODOLOGIES, PROCESSES AND CRITERIA TO IDENTIFY FRAGRANCE ALLERGENS OF CONCERN

31 October 2012

BACKGROUND

Based on regular contacts with EU Commission (DG Sanco) and the conclusions of the Public Hearing on Fragrance Allergens which took place on March 5th, 2012, the Industry understood the need for further scientific work enabling the definition of explicit criteria and the clarification of identified areas of concern in order to provide an agreed and transparent framework for assessing fragrance ingredients in a prospective way.

This work does not only concern the Fragrance Industry but embraces multi stakeholders, including Academia, the relevant services of the EU Commission, Dermatologists and the Downstream User Industry.

This need for clarity was already highlighted in the first part of the draft Industry proposal presented to the EU Commission on April 13th, 2012. The items of this final Industry proposal for a joint work plan related to risk assessment are:

- Definition of fragrance allergens
- Definition of fragrance allergens of specific concern
- Pre-haptens
- Pro-haptens
- QRA

THE STRATEGIC INTENT

The strategic intent of this proposal is to **prevent further uncertainty** for the fragrance and downstream industries in an area which is critical to consumer safety. It is also intended to provide the industry with a better visibility for business continuity. Indeed, it is vital for business to rely on a robust prospective risk assessment approach securing the most predictive extrapolation in the area of fragrance allergy. This scientific approach should also take into account the relevance of its findings in real life, through regular review. This is critical to enhance consumer confidence in the safe use of products. In addition, without such a prospective approach, the current situation could jeopardize investments in innovation and leading to a significant loss of added value and competitiveness for business.

IDEA MANAGEMENT TEAM
Avenue des Arts 6 / 1210 Brussels, Belgium
Tel: +32-2 214 20 61 / Fax: +32-2 214 20 69 / www.ideaproject.info

THE WORK PLAN

This document represents the proposal for a scientific work plan, which is intended to lead to a shared common understanding of methodologies, processes and criteria, and could become the basis of a robust approach for a multi-stakeholder risk assessment program.

The work plan proposes **four specific tasks** which should be addressed in order to develop a common understanding of the risk assessment process:

- **Task I:** Define the concept of 'fragrance allergens'
- **Task II:** Define the concept of 'allergens of specific concern'
- **Task III:** Address the specific problem of pre- and pro-haptens
- **Task IV:** Address the validity of the QRA methodology and the possibilities of further refinement

In combination, these tasks should set an open and transparent dialogue which should lead to a comprehensive understanding of fragrance allergens and the assessment of their risk to the population.

The aim of the workshops and the whole program is to lead to procedures and guidance documents for all parties involved. Those guidance documents, if meaningful and efficiently applied, should help create the required certainty in the evaluation process and master the management of fragrance allergens in the future.

The overall timeline of accomplishing all 4 tasks is assumed to be about 3 to 7 years. For the completion of the technical aspects a minimum time period of 3 years is foreseen and additional time will be needed to discuss and translate agreed actions into a framework that will provide all stakeholders involved with a secure business environment in which to operate in the future.

Some tasks should be able to be addressed in a much shorter timeframe, especially as those will be the basis for other tasks. This is especially true for task 1, which should be able to be completed within about a year. A more detailed outline of timelines, organizational aspects and deliverables will be presented in a separate document.

All tasks may require a series of workshops, but only if necessary. If the goal of the task can be achieved in one workshop this will be the end of the task.

THE SUPERVISORY PROCESS

In order to secure the optimal governance of the project, it is foreseen to nominate a Supervisory Group. Its mission would be to supervise the process and to ensure the scientific integrity and the full transparency of the overall project.

The Supervisory Group (SG) would be composed of 5 to 7 members with no vested interests in Industry activities. The members would be jointly nominated by the EU Commission and IFRA.

The remits of this group would be to scrutinize all aspects of the work plan implementation in order to guarantee the neutrality of scientific debates and experts' selection procedures. The Supervisory Group would review the draft agenda and related activities.

Furthermore, for each workshop, the Supervisory Group would nominate a rapporteur amongst its members. This rapporteur would attend the workshop and, assisted by IFRA project management, write the report based on its outcome. This progress report would be reviewed by the Supervisory Group to draw conclusions and set recommendations in view of improving the overall process.

THE MONITORING PROCESS

We recommend, in partnership with DG SANCO, to host an annual review on fragrance allergens. The review is aimed to **monitor and validate the progress made** by the experts and to **update the program and priorities** when needed. Rapporteurs of the workshops held during the year will present their reports at this occasion. This event will be the appropriate platform to ensure that **all stakeholders can express their views and ask questions.**

As stated before, the Industry must engage with a broader group of stakeholders. This group will inevitably bring with it a variety of perspectives and positions. This collaborative effort will not only result in a stronger method of managing allergens, but will also build a lasting relationship which may serve as a model for other fragrance associated topics relating to the on-going enhancement of consumer safety.

The yearly review organized under the auspices of the EU Commission will involve broad stakeholder participation with the aim to build a common understanding of fragrance allergens and implement a new integrated forward looking management process, based on a number of components that can easily be enacted.

The first review will serve as a kick off for the series of workshops end of 2012 or early 2013.

The participation in the Review should be globally oriented as the topic of fragrance allergens is not limited to Europe and such a fundamental discussion should be carried out with a global perspective. Therefore we would suggest inviting also members of the International Cooperation on Cosmetic Regulation (ICCR).

TASK I: DEFINE THE CONCEPT OF FRAGRANCE ALLERGENS

I.1 - WHY DO WE NEED A DEFINITION OF FRAGRANCE ALLERGENS?

Some fragrance ingredients have the potential to cause dermal sensitization. However, such fragrance allergens may be described in various ways, so there is a need to define them via a collaborative approach between stakeholders to ensure that effective consumer safety can be delivered.

A clear understanding of what is a skin sensitizer and what are the tools to identify it remains a prerequisite to define a fragrance allergen. Allergy includes two phases:

- Induction of specialized immunological T cell memory in an individual by repeated exposure to an allergen (i.e. the immune system learns to react).
- Elicitation, i.e. production of an immune system (T cell) mediated allergic response subsequent to exposure of a sensitized individual to the allergen (visible skin reaction). Usually, lower doses are necessary for elicitation than are required for induction.

Skin sensitization is not an 'all or none' phenomenon: there is a sequence of immunobiological events that need to be activated to produce first an induction of sensitization and secondly to elicit a clinical reaction.

In consequence, induction and elicitation of contact allergy are threshold phenomena and allergic contact dermatitis therefore is to a considerable extent a preventable disease.

I.2 - WHAT ARE THE DIFFERENT OPTIONS?

The simplest level of definition is by hazard classification. There exists already a formal definition of substances, including fragrances, which present an allergenic hazard, under the UN GHS and EU CLP regulations. This definition is primarily developed to protect workers handling raw materials. This may result in the classification of a substance used in fragrances as a skin sensitizer, which is important to ensure correct classification & labeling and subsequent handling during manufacturing. This approach also has implications for the labeling of some consumer products, for example detergents in the EU.

The UN GHS criteria are certainly a useful element to take into consideration but insufficient for addressing the full scope of the topic as it is only a hazard assessment tool.

Several in vivo test methods have been used to identify skin sensitizers. Traditional guinea pig methods identify allergenic hazard based on the % of animals exhibiting a response after repeated applications of the substance at a fixed concentration. However, guinea pig tests are not designed for the determination of potency, although in the recent ATP to the CLP Regulation a scheme is proposed to distinguish between two potency categories based on guinea pig data. In contrast, the murine LLNA is more widely used not only to determine the potential of a material to induce contact sensitization, but also for the measurement of the relative potency. Much work has been done to

correlate the dose-response data obtained in the mouse LLNA with what is known about potency in humans.

Of great relevance in the near future is the development and validation of in vitro methods, since this area is progressing rapidly, being one of the most important research topics nowadays linked to skin sensitization. How these methods will deliver potency as well as hazard information is a key question of relevance to risk assessment.

Another important element in understanding skin allergies is clinical (patch test) data. As recently pointed out by Basketter and White in the Editorial to Contact Dermatitis (**2012**, *Contact Dermatitis*, **67**, 1-2), for the dermatologist facing a patient with a suspected allergic contact dermatitis, the application of a baseline patch test series, often supplemented by additional selected substances based on the patient's history, represents a key component of their diagnostic 'toolbox'.

Initial patch test data provide the information that these materials are contact allergens. A comprehensive risk assessment system therefore has to include them as an important alert instrument since diagnostic patch test data offer:

- an indication that exposure to a substance may cause allergy in the population
- a means to compare the relative importance of contact allergens in terms of the frequency of reactions
- a means of following contact allergy trends over time

The recently published SCCS Opinion contains a classification of (fragrance) allergens using the number of positive patch test results from clinics as the qualifying element.

Research has been initiated to further refine the patch testing protocol (execution, standardization of patch test material, verification of reactions as allergic rather than irritating). This is important work that will help provide additional value to this important instrument.

It is well recognized that positive patch tests identify whether a patient has contact allergy to a substance, (with the exclusion of false positive patch tests are correctly identified), but do not directly determine whether it has relevance for the eczema that led to the consultation. It does not identify what exposures caused the induction of contact allergy (e.g. natural versus consumer product exposure, or which product type) nor does it give any dose-response information or inform on what types of exposure may be tolerated This must be derived from the clinical history (anamnesis), evidence of relevant exposure, the experience of the dermatologist and more importantly through use tests such as (repeated) open application tests.

A comprehensive risk assessment approach should therefore also include the thorough consideration of the aspect of clinical relevance.

Finally, other information, not adequately incorporated so far, and that could be of relevance, e.g. cosmetovigilance data from consumer product companies and/or poison centers, are also important when identifying the existence or emergence of allergy in consumers.

I.3 - RECOMMENDED ACTIONS

Industry, the dermatological community, and regulators need to work together to find a common ground and understanding of how to best integrate clinical (and cosmetovigilance) data into the risk assessment process.

The industry is proposing a new approach to bring the stakeholder input together in a collaborative program, with a structured framework that will enable more effective dialogue but also clearer approaches to defining allergens as well as processes to assess their risk. It is envisaged that this would be managed with a combination of industry/non-industry toxicologists, clinical and experimental dermatologists as well as risk assessors, to enable a comprehensive, robust and pragmatic weight of evidence based approach to address the risks deriving from fragrance allergens.

TASK II: DEFINE THE CONCEPT OF 'ALLERGENS OF SPECIFIC CONCERN'

II.1 - WHAT DO WE MEAN BY ALLERGENS OF SPECIFIC CONCERN?

The need is to agree on criteria for the identification of a (fragrance) allergen, which would define how to identify a 'significant risk to the general population'.

Industry, the dermatological community, and regulators will work together to find a common ground and understanding on how to integrate clinical, cosmetovigilance and exposure data into the risk assessment in order to produce an accurate definition of "allergens of specific concern". For instance, different levels of concern may be defined:

- Magnitude of the issue (low, medium or high percentage of population effected)
- Categories of allergens (all sensitizers, rare allergens, common allergens, allergens of (very) high concern, etc.)
- Sources and levels of exposure

In this respect there is a need to address questions related to the above definitions such as what defines a substance for which a risk assessment technique such as the QRA (based on avoidance of induction) is considered sufficient versus what defines an allergen for which other more restrictive measures need to be considered necessary.

II.2 - WHAT SHOULD BE DISCUSSED AND RESEARCHED WITHIN THE RISK ASSESSMENT PROCESS?

Several areas of the risk assessment process require further refinement and understanding to allow their integration into a common methodology. This need is particularly true for the exploitation of data that underline the definitions of fragrance allergens and allergens of specific concerns:

- **Use of toxicological data:** This generally addresses primary prevention by attempting to identify safe exposure levels, which avoid the induction of skin sensitization. The QRA approach is clearly defined and published and is the basis of the existing IFRA Ingredient Standards on sensitization. However, there are still areas for further research and potential improvement (e.g. consideration of aggregate exposure). This is part of the fourth task.
- **Use of clinical data:** Data from dermatology clinics is at the forefront of the identification of substances that cause allergy in the general population. However, dermatologists are not routinely included in the discussion on risk assessment. In addition to the interpretation of data, including dermatologists in active consideration of approaches to risk assessment will provide for a collaborative approach to establishing safe use conditions. The following aspects need to be considered in incorporating correctly use clinical data in the risk assessment process:
  - Determination of contact allergy via the use of the patch test and whether there is a need for refinement to this tool (e.g. Nosbaum et al, 2009).

- Differentiation of cases with likely induction of sensitisation by the ingredient from cases with likely cross-reaction in elicitation (with allergy induced by a different chemical).
- The relationship between patch test exposure conditions and real life exposure (e.g. Maibach et al.) and clinical relevance of a positive patch test response (e.g. Ale and Maibach, 2010; DeGroot 1999, EDEN study data)
- Consideration of a scientific study to investigate the clinical relevance of positive patch tests.
- Definition of levels of concern: A clear definition is required to identify levels of concern of allergens. For instance, this definition may be based on an absolute number or percentage of patients within dermatological clinics reacting to a substance, number of clinically relevant cases per year, percentage of general population with (clinically relevant) reactions, etc. It might further be worthwhile to discuss cases of sensitization in relation to the marketed amount of an ingredient and use levels or more sophisticated stochastic analyses like allergy incidence in predicted exposed subpopulations.
- Potential role of alternative techniques to patch testing (like immunologic systems).
- Potential role of sample provision to dermatologists to facilitate diagnosis (is the system sufficiently effective?).

- **Use of Cosmetovigilance data:** Cosmetovigilance data is an important source of information that is mostly held within consumer product companies, but can be used to identify emerging issues or substances of concern. The availability and quality of this data needs to be further explored to understand the potential usefulness of such data within this process. Consumer product companies could consider sharing data perhaps through a third party (to protect confidentiality), to enable a broad on-going use of sensitization incidence information to drive prioritization and decision making.

II.3 - CONSIDERATION ON THE USE OF ELICITATION THRESHOLDS FOR RISK ASSESSMENT

Discussion is needed on reliable protocols/measures to determine those thresholds and how far elicitation thresholds could be a relevant and reliable model for use in risk assessment. One focus should be comparing thresholds from ingredients with different potency, particularly weak sensitizers, the category that contains the majority of fragrance sensitizers.

The Research Institute for Fragrance Materials (RIFM)[i] is actively engaged in an elicitation threshold study for Eugenol, which could further inform these discussions. Insights from the already initiated Repeated Open Application Test (ROAT) with Oakmoss (containing atranol and chloroatranol) could also prove helpful.

We recommend that the appropriate use of elicitation thresholds for risk assessment be discussed and protocols/measures be agreed to determine them. The organization of a workshop of experts seems to be the best option to address the questions outlined above.

TASK III: ADDRESS THE SPECIFIC PROBLEM OF PRE- AND PRO-HAPTENS

III.1 - WHY DO WE ADDRESS PRE- AND PRO-HAPTENS UNDER THE SAME TASK?

The issues around pre- and pro-haptens have been highlighted and it is important to find a common agreement on how to assess the risk related to these materials.

By definition both pre- and pro-haptens are not allergenic themselves but can give rise to allergenic species. According to the general understanding:

- a pre-hapten is a chemical substance that can be transformed into an allergenic species via abiotic processes;
- a pro-hapten is a chemical substance that can be transformed into an allergenic species by the action of skin enzymes.

It is important to understand that the discrimination between pre- and pro-haptens cannot always be made and it is quite common that a chemical substance be converted into a hapten both via biotic and abiotic pathways (e.g. hydrolysis and oxidation can happen both biotically or abiotically). Given that the resulting hapten is often the same regardless of the conversion pathway, we recommend to use the term “abiotic/biotic transformations” rather than pre- and pro-haptens.

III.2 - WHAT SHOULD BE DISCUSSED WITH REGARD TO ABIOTIC TRANSFORMATION?

Air oxidation can transform benign fragrance ingredients into allergenic species. A substantial body of research (mainly publications by A.T. Karlberg), partly funded by the fragrance industry, to identify the allergenic species resulting from oxidation has been carried out. Industry has collected information on the presence of oxidized materials in fragrance raw materials, compounds and finished products, both unopened and after being opened and used for up to five years. Such analytical information of ‘real life exposure’ in combination with clinical data helps to understand the importance of this mechanism. However, many knowledge gaps remain. Therefore, we recommend that a dialogue be established to discuss the need for additional research on the abiotic transformation. The questions to be addressed can be divided into two categories:

Technical questions related to the manufacturing process:

- A research program, e.g. a stability study and analysing for intermediates and by-products of the short-life hydroperoxides could be considered.
- Should such a study have specific focus (targeted peroxides and by-products) or a broad focus (determine general peroxides values)? Is it sufficient to have the key focus on hydroalcoholic products or does it needs to be enlarged to cover other product forms? Are there product categories of specific concern (Skin creams, Hair dyes, Deodorants)?
- Should aromatherapy products get included in the investigations as consumers can be exposed to higher doses of putative pre-haptens in these products?

- Is there sufficient protection of typical consumer products against the risk of abiotic transformation? What value do the measures have that already have been put in place by Industry (product format, antioxidants, etc.)?
- How does 'maturation' happen, under which conditions does it usually take place, and does it potentially lead to peroxide formation?

Toxicological questions:

- Scope – is it justified based on experience to consider terpene peroxides to be a relevant cause of allergic contact dermatitis through the use of cosmetic products?
- What information does patch testing with oxidized materials provide?
- Clinical relevance – can observed patch test reactions be linked to consumer products containing oxidized materials? Could high exposures to oxidized materials stimulate various T-cells to react to give rise to non-specific elicitation reactions?
- Commission independent laboratories to determine the presence of oxidized linalool or limonene. What other exposures should be considered?
- Standardization of oxidized patch test material – how to ensure that all dermatologists test with the same material. Should we envisage testing only with defined hydroperoxides instead of an oxidation mixture?

Given the complexity of this debate, we suggest that a workshop be organized with experts to clearly define what the issues are and how to progress and manage them.

III.3 - WHAT SHOULD BE DISCUSSED IN RELATION TO THE HYDROLYSIS ISSUE?

Some fragrance ingredient categories (esters, acetals, Schiff bases) can undergo a biotic or abiotic transformation of hydrolysis to produce a skin sensitizer. Depending on the degradation pathway (biotic or abiotic), the suggested actions differ:

III.3.1 - ABIOTIC TRANSFORMATION

In the case of hydrolysis we know what would be the potential allergen formed and its potency. Formation of this allergen during production and shelf life can be monitored, and it would therefore be possible, based on historical or analytical data, to determine the risk of hapten formation by hydrolysis, taking into consideration the complexity resulting from various product categories. It is important to notice that each ester (or acetal or Schiff base) has its own chemical reactivity, and kinetic studies may lead to an enhanced understanding of the hydrolysis issue. The outcome of such studies would be the estimated probability to observe hydrolysis products for a given material in a given matrix.

As mentioned under item III.2, an in-depth dialogue between experts, starting with a workshop and followed by research options, may be necessary to define these issues and how to manage them.

III.3.2 - BIOTIC TRANSFORMATION

Less information is available on whether hydrolysis in the skin is an important mechanism, especially on the kinetics of this process. Limited studies with isolated rat skin cytosol and rat skin microsomes on Isoeugenyl- and Eugenyl-acetate indicate that these esters do not fully hydrolyse in a time-dependent manner. This preliminary study did not give clear-cut answers and confirmatory results are needed.

Kinetic and skin penetration studies should be a key to understand what happens on the skin. Isoeugenyl esters may be a possible starting point as they are the sole materials for which significant rates of positive patch tests have been reported. The data resulting from these studies should be of help to answer the following questions:

- Scope – is it justified based on experience to predict biotic transformation to be a relevant cause of allergic contact dermatitis through the use of cosmetic products?
- What is the ratio of biotic versus abiotic hydrolysis? What are the percentages of observed reactions due to biotically-generated haptens versus abiotically-generated haptens?

TASK IV: ADDRESS THE VALIDITY OF THE QRA METHODOLOGY AND THE POSSIBILITIES OF FURTHER REFINEMENT

IV.1 - WHERE IS THE FRAGRANCE INDUSTRY WITH THE QRA TODAY?

The QRA approach is considered by the industry as an important step forward in dermal sensitization risk assessment, and the method, first published in 2001 (Gerberick et al., Contact Dermatitis, 45:333-340) has been implemented by the fragrance industry since 2006. An update has been published in 2008 (Api et al., Regulatory Toxicology and Pharmacology, 52:3-23) and the QRA Expert Group[ii] encourages further refinement to the QRA for fragrance ingredients. Some areas of improvement are considered below.

- **Consumer Exposure:** Improved exposure data (Hall, 2011) is being incorporated into the QRA methodology. In addition, RIFM has sponsored work to investigate the effects of aggregate dermal exposure. The outcome of this work is being accounted for in the methodology and we suggest that an open discussion be held on the validity of the QRA and on this initiative in particular.
- **Safety Assessment Factor (SAF):** A paper which specifically addresses the use of uncertainty factors in QRA for skin sensitization has been published (Felter, et al., Contact Dermatitis, 2003, 47:257-266). However it is acknowledged that further dialogue on SAFs would be appropriate. This would include better clarification of what the SAFs are applied to (e.g. not to clinically diseased skin).
- **Acceptable Exposure Levels (AEL) and Exposure Data:** A more detailed explanation of AELs and how they are applied should be provided. There also is a need for more details on the pragmatic approach and a review of aspects of having high calculated values in (mainly) rinse-off products.
- **Current boundaries of the QRA:** While occupational exposures to consumer products can be an important source of exposure they are not considered in the current QRA. This mainly stems from a lack of adequate exposure data. Furthermore the QRA methodology does not cover aromatherapy (neither workers nor customers). These currently not reflected exposures remain a potential area of research.
- **Use of Diagnostic Patch Test Data and Retrospective Analysis:** Diagnostic patch test data from dermatology clinics are not used in the primary determination of safe use levels based on induction. This is because these data are a measure of elicitation of allergic contact dermatitis, not induction. Nevertheless, the diagnostic patch test data provide feedback on whether thresholds of used based on the QRA has been correctly established (see Task II.2).

  A review of retrospective data for three fragrance ingredients has been published (Api et al., 2010). Retrospective review of other fragrance ingredients and other non-fragrance ingredients should also be considered.

  Thus, clinical results from the dermatology community (including targeted studies) and company post-market surveillance data should be used to evaluate the effectiveness of QRA-based interventions.

IV.2 - RECOMMENDED ACTION

The best way to address the validity of the QRA methodology and the possibilities of further refinement would be to organize an in-depth dialogue between experts. We recommend that a specific workshop be held on the QRA methodology.

[i] The Research Institute for Fragrance Materials (RIFM) is a non-profit scientific institute founded by the Fragrance Industry in 1966 for the purpose of generating and evaluating safety data on fragrance ingredients. The scientific foundation of RIFM is built around its independent Expert Panel (REXPAN). It is comprised of internationally known academic dermatologists, pathologists, toxicologists and environmental scientists, none of whom has any other connection to the fragrance industry, and whose work involves the safety evaluation of fragrance ingredients under conditions of intended use. Additional expertise is provided by adjunct groups with knowledge in genetic toxicity, respiratory science, reproductive effects, environmental fate and epidemiology. The results of their evaluations are published in peer-reviewed scientific journals, and their decisions regarding restrictions of use are promulgated through the IFRA Standards.

[ii] The QRA Expert Group is a RIFM Task Force of ten toxicologists from the fragrance and the downstream users industry. This group worked on the adaptation of the QRA methodology to the Fragrance Industry and continues to watch the outcome of the QRA implementation in view to improve the model.